REMARKS

In view of the following remarks, the Examiner is respectfully requested to allow Claims 1-18 and 24-28, as well as newly presented Claims 29 -33, the only claims pending and currently under examination in this application.

In the above amendments, Claims 1, 6, and 11 have been amended to delete the phrase "only acts locally". Support for the deletion can be found in the claims as originally filed. In addition, the claims have been amended to specify that the NSAID is anti-inflammatory, support for this amendment may be found at page 6, line 14. Newly presented Claims 29 to 30 find support on page 8, lines 25-28 of the specification. Newly presented Claim 31 finds support on page 7, lines 19 to 22. Newly presented Claims 32 to 33 find support in originally filed Claim 10. As the amendments introduce no new matter, their entry by the Examiner is respectfully requested.

The Examiner is thanked for withdrawing the § 103 claim rejection over Freidman in view of Oda.

The Examiner is also thanked for the helpful personal interview held with the undersigned on July 14, 2008. During the interview, the above amendment to Claim 1 was discussed with respect to the pending rejection under 35 U.S.C. 112, first paragraph rejection. The Examiner agreed that the above amendment would overcome the rejection and, if made, the rejection would be withdrawn. In addition, the newly cited combination of references was discussed. The undersigned explained that the newly cited combination of references still do not teach or suggest all of the elements of the claimed invention and further that the previously filed declaration evidencing unexpected results overcomes the newly presented obviousness position. The Examiner agreed to consider the position of the Office further upon filing of a formal response. It is believed that the above paragraph provides an accurate and complete summary of the matters discussed during the interview.

Claim Rejections - 35 U.S.C. § 112

Claims 1-18 and 24-28 are rejected under 35 U.S.C. § 112, first paragraph, as reciting "only acts locally," a term which the Examiner regards as failing to comply with the written description requirement.

Without conceding as to the correctness of this rejection, and solely in the interest of expediting prosecution, the independent claims have been amended to delete the phrase "only acts locally," thereby rendering this rejection moot.

Claim Rejections - 35 U.S.C. § 103

Claims 1-18 and 24-28 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the combined teachings of either the article by Pradalier et al. or the article by Cluff, each combined with both US 5,667,799[1] to Caldwell and US 5,318,960 to Toppo. This rejection is respectfully traversed as applied and as it may be applied to the amended claims.

In making this rejection, the Examiner asserts that the claims are rendered obvious by Pradalier and Cluff's use of oral NSAIDs for the treatment of migraines, Toppo's topical delivery of NSAIDs at the site of arthritis pain, and Caldwell's delivery of local anesthetic agents to the keratinized skin proximal to target nerves associated with migraines. See Office Action, paragraph bridging pages 6 and 7. The Applicants note that, contrary to the Examiner's assertion on page 7, lines 2-6 of the Office Action, Caldwell does not teach delivery of NSAIDs to the keratinized skin, but instead teaches application of a local anesthetic to a specific local region of the keratinized skin associated with the location of particular nerves. Local anesthetics belong to a different drug class that NSAIDs and operate by a mechanism of action that is distinct from the mechanism of action of NSAIDs. Specifically local anesthetics operate by interacting with sodium channels within nerves. NSAIDS do not interact with sodium channels. See e.g.,Remington, The Science and Practice of Pharmacy (19th Edition, Mack Publishing 1995) at page 1146 (which describes the mechanism of action of local anesthetics as nerve conduction blockers in Col. 1) and at page 1208 (first paragraph of Col. 1 which

[1] The Applicant notes that US 6,667,799 is mistakenly cited instead of 5,667,799 in the Office Action.

states that the target of NSAIDs is inhibition of prostaglandin synthesis).

The Applicants submit that the combination of the references does not render the claimed invention obvious because:

1) the combination of the cited references fails to teach or suggest each and every element of the claims; and
2) the combination of the cited references fails to provide one of skill in the art with predicted success in the claimed invention.

The combination of references fails to teach or suggest each and every element of the rejected claims.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claimed elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1).

The claimed invention is directed to methods of ameliorating headache pain caused by a migraine headache, indomethacin responsive headache syndrome, tension headache, or cluster headache by topical delivery of an NSAID. The claimed methods as amended include: "topically applying an anti-inflammatory effective amount of a topical NSAID formulation comprising an NSAID as the only active agent present in said topical formulation to a keratinized skin surface of the head of said host." As such, an element of the claimed methods is topically applying a topical formulation of an NSAID which works via a local anti-inflammatory mechanism (non-systemic) to a keratinized skin surface of the head.

When treating a headache with a topical NSAID formulation, meaning only consisting of a local effect (not systemic), only local action of the active agent of the topical formulation is responsible for the treatment effect. In the keratinized skin surface of the head, the claimed topical formulation of NSAID acts only locally at the site of application, as opposed to systemically in the body. As developed below, this element of "topically applying an effective amount of a topical NSAID formulation" of the claims is neither taught nor suggested in any of the cited combination of references nor can this

invention be predicted from their combined teachings.

As acknowledged by the Office, the cited primary references of Pradilier and Cluff are silent with respect to topically applying a topical NSAID formulation as claimed. Nor do the cited Toppo and Caldwell references make for this deficiency in the teachings of the primary references.

Toppo is directed to an NSAID composition for relief of arthritis-related pain (col. 1, lines 20-25). Importantly nowhere does Toppo describe the utility of a topical NSAID applied to the keratinized skin of the head to relieve headache. Toppo is a composition patent that focuses on the treatment of arthritis, which has a completely different underlying pathophysiology and location of pain than migraine and other headache disorders.

In contrast, the rejected claims are directed to treating a headache by topical delivery of an NSAID applied to the keratinized skin of the head. The claimed invention is based on the surprising and unexpected discovery of a topical NSAID formulation, which, upon application to the keratinized skin of the head, does not produce any meaningful systemic blood levels (i.e., orders of magnitude below that produced by administering a therapeutic oral, rectal, or intravenous dose of the same medication) and results in alleviation of headache pain, i.e., pain perceived to be in the brain. The inventors of the present application found that, contrary to the accepted belief of those of ordinary skill in the art at the time the application was filed, one could treat the migraine headaches and indomethacin responsive headaches and reduce the pain felt in the brain by applying a topical NSAID formulation to a keratinized skin surface of the head, e.g., the forehead and/or temple, resulting in only local action of the NSAID.

Moreover, it is not obvious to those knowledgeable in the art of treating headache conditions that successful treatment by systemic delivery oral composition of an NSAID would suggest successful treatment by a topical formulation of an NSAID that works only locally by applying it to the keratinized skin surface of the head. Oral and rectal NSAID delivery composition that affects systemic circulation is completely distinct from a topical formulation that acts locally and does not produce any meaningful NSAID drug levels in the systemic circulation. Furthermore, at the time of this invention, headache authorities did not nor would not have conceived of treatment by applying an NSAID topically to the

keratinized skin surface of the head whereby the NSAID acted only locally because (1) authorities in the field believed the underlying biologic/pathophysiologic mechanism of migraines, indomethacin-responsive headaches, central tension type headaches, and other headache conditions were related to abnormalities solely within the brain and (2) NSAIDs would only successfully treat headache symptoms if large, clinically meaningful blood levels were achieved. Topically delivered drugs result in systemic drug levels orders of magnitude less than those achieved by intravenously, orally, or rectally delivered dosing and are believed to not result in any clinically meaningful blood levels that would have any effect within the brain. In fact, oral NSAID studies have shown a dose-response relationship, meaning that at low oral doses that result in low systemic blood levels, no or minimal (not clinically meaningful) headache pain relief is experienced by the patient- a certain 'threshold' blood level is needed for a clinically meaningful affect. The blood levels achieved by topical NSAID treatment are well below these needed systemic levels. See e.g., Laska et al., Clin Pharmacol Ther. 1986 Jul;40(1):1-7 where the authors conclude that "Our results support the proposition that increased ibuprofen (an NSAID drug) serum levels lead to increased analgesia (pain relief)."

Thus, the combined teachings of Pradaleir, Cluff, and Toppo do not teach or suggest the claimed topical method for treating headache.

Caldwell is directed to a pain relief composition that includes a local anesthetic (abstract). According to Caldwell, "local anesthetics by themselves do not readily penetrate the keratinized layer of the skin" (col. 1, lines 54-55). In order for the anesthetic to penetrate the skin, Caldwell's composition requires a penetration enhancing agent(s) such as eucalyptol. Upon application, the local anesthetic agent penetrates the keratinized skin surface so as to interact with underlying specific nerves and blocks conduction in the target nerves (col. 2, lines 46-51).

Caldwell's teaching is the treatment of headache by occipital and/or supraorbital nerve block via the precise application of the specific topical local anesthetic formulation over the areas where these nerves can be affected. The precise supraorbital nerve region where a nerve block is performed is shown in the below picture:

The occipital region where a nerve block is performed is shown in the below diagram (from www.postgradmed.com/issues/2004/09_04/ashkenazi3.gif):

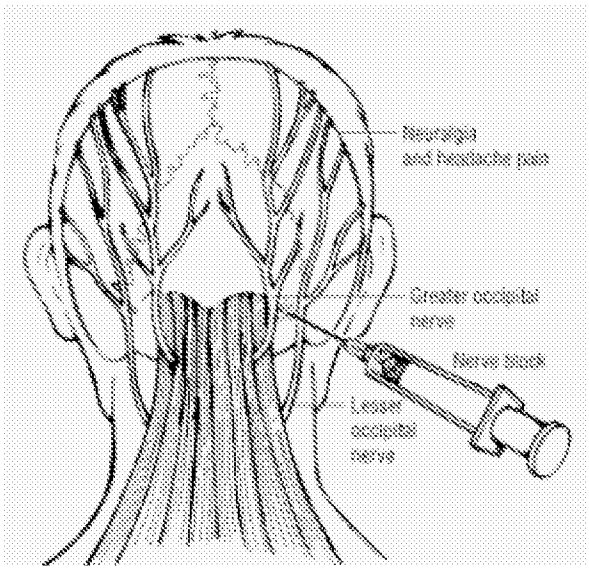

Figure 3. Occipital nerve block. Via a needle inserted at the base of the skull, an anesthetic agent is injected around the origin of the greater occipital nerve.

Importantly local anesthetics cause a reduction in nerve impulses by binding to sodium channels on the nerve (resulting in "numbness"), whereas NSAIDS reduce inflammation and do not bind to sodium channels. Thus the current invention differs from Caldwell by employing a completely different type of agent which operates by a completely different mechanism.

Accordingly, the combination of references fails to teach or suggest topically applying a topical NSAID formulation as claimed.

Because the Caldwell reference is directed to the use of a completely different type of active agent from an NSAID that operates by a completely different mechanism, one of skill in the art would not extrapolate any teaching of Caldwell to the teaching of the other references to topically apply an NSAID as claimed. As such, contrary to the Examiner's position as set out in the Office Action, it would not be obvious to topically apply an NSAID as claimed because an NSAID is a completely different type of active agent from a local anesthetic.

The combination of the cited references fails to provide one of skill in the art with predicted success in the claimed invention.

The Applicants further contend that the combination of the cited references fails to provide one of ordinary skill in the art with predicted success in the claimed invention.

In addition to demonstrating that all elements were known in the prior art, the Office must provide evidence that the combination would be "a predicted success". This principle is illustrated in *three* Supreme Court cases[2] decided prior to *KSR*, and is a recurring theme of *KSR*. For example, in *KSR*, the Supreme Court stated that in order for a combination of elements to be patentable, "the combination must do more than yield a predictable result". [3] Likewise, the corollary principle, namely that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"[4] is also discussed. The Supreme Court in *KSR* also stated that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions".[5]

Thus, according to the Supreme Court, an analysis of the "predictable success" of a combination of known elements may be used to separate patentable combinations (e.g., a battery that contains water, in the case of *United States* v.

[2] *United States* v. *Adams*, 383 U.S. 39, 40 (1966); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.C. 57, 60-62 (1969); and *Sakraida* v. *AG Pro, Inc.*, 425 U.C. 273, 282 (1976).
[3] *KSR International v. Teleflex Inc.,* 127 S. Ct. 1727, 1740 (2007).
[4] *KSR International v. Teleflex Inc.,* 127 S. Ct. 1727, 1739 (2007).
[5] *KSR International v. Teleflex Inc.,* 127 S. Ct. 1727, 1740 (2007); emphasis added.

Adams, *supra*) from those that are unpatentable (e.g., an adjustable pedal having a fixed pivot point and a sensor, in the case of *KSR, supra*).

MPEP § 2145 sets out the principles in considering rebuttal arguments by applicants against obviousness, stating in part that: "Rebuttal evidence may also include evidence that the claimed invention yields *unexpectedly improved properties or properties not present in the prior art*. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties" (emphasis added).

As mentioned earlier, the results of this invention were unexpected and surprising based on knowledge and the state of the prior art among the headache scientific and clinical community.

Both Pradalier and Cluff merely disclose the general use of oral NSAIDs for the treatment of migraines, well known to the authors and other headache experts that a necessary oral dose resulting in a necessary systemic NSAID blood level is required in order to achieve relief of headache pain; (thus why this invention represents unexpected and surprising results). Furthermore, both Toppo and Caldwell do not teach topical delivery of an NSAID to the keratinized skin surface of the head for the relief of headache pain.

Toppo only discusses the relief of arthritis pain. Caldwell is concerned with delivery of a local anesthetic, a different type of medication from NSAIDs that works via a completely different mechanism. One of skill in the art reading the above four references would not be able to predict success in making a topical formulation of NSAIDs as claimed for relief of headache via application on the keratinized skin surface of the head. Toppo does not mention a keratinized skin surface of the head or the condition of headache. Caldwell uses a different medication that has a different mechanism of action.

Further, as the Applicants established in the previous response and the accompanying declaration by Lawrence C. Newman, M.D., (a copy of which is attached) that, prior to the Applicants' work reported in the Specification, the

common belief in the relevant art was that a topical formulation of an NSAID that is effective by acting only locally would not be able to supply a therapeutically effective level of the NSAID sufficient to treat a headache and that only local peripheral action of an NSAID drug applied to the skin of the head would not treat headache pain. The present invention is based on discovery of the unexpected result that a topical formulation of an NSAID applied to the keratinized skin of the head does indeed provide a therapeutically effective method of treating headaches.

As such, one of ordinary skill in the art, even in view of Pradalier, Cluff, Toppo, and Caldwell, would not reasonably expect that a topical formulation of an NSAID topically applied to the head area in a manner that it acts only locally could treat headaches with predictable success under the *KSR* standard.

In light of the above arguments, it is submitted that: 1) the combined teachings of the references fail to teach or suggest all elements of the claimed methods; and 2) the cited combination of references fails to provide the requisite predicted success in the claimed invention. Accordingly, Claims 1-18 and 24-28 are not obvious under 35 U.S.C. § 103(a) over the combined teachings of either the article by Pradalier or the article by Cluff, each combined with both Caldwell and Toppo, and this rejection may be withdrawn.

Finally, newly presented Claims 29 to 33 are patentable for at least the reasons provided above. For example, Claims 32 and 33 specify placement on the forehead or temple, which is a completely different location from that disclosed in Caldwell. See above diagram illustrating the occipital and supraorbital regions.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, the action that is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, reference no. TOPI-002CIP.

Respectfully submitted,

Date: August 1, 2008

By: /Bret E. Field, Reg. No. 37,620/
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Enc:

- Declaration by Larry Newman
- Remington, The Science and Practice of Pharmacy (19th Edition, Mack Publishing 1995) page 1146 and 1207-1208

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